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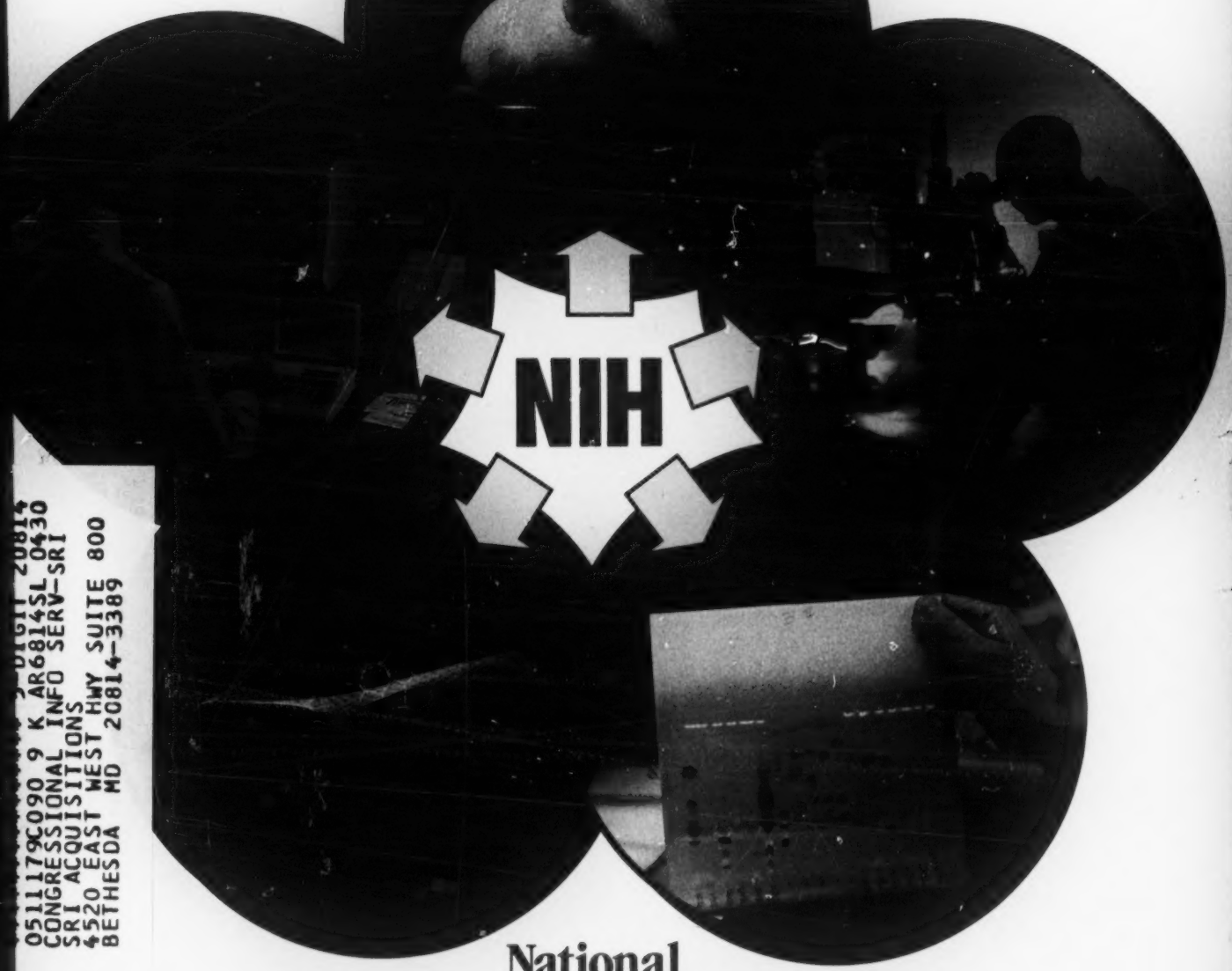
APRIL 2, 1990

CHEMICAL & ENGINEERING

NEWS



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National Institute of General Medical Sciences funds variety of chemical research Page 13

CHEMICAL & ENGINEERING
NEWS
APRIL 2, 1990

Volume 68, Number 14
CENEAR 68 (14) 1–48
ISSN 0009-2347

News of the Week

■ **Two U.S. chemical companies have refused to sell the Army a key precursor chemical needed to make the nerve gas Sarin.** Page 4

■ **DOE studies possible buildup of flammable hydrogen gas in nuclear waste storage tanks at Hanford, Wash., facility.** Page 5

■ **Under a new initiative from NSF, states will receive grants to promote reform in precollege science and math education programs.** Page 5

■ **Study of 10 years of global temperature measurements collected by satellite shows no warming trend for Earth during the 1980s.** Page 6

■ **Cetus and Genetics Institute have resigned from the Industrial Biotechnology Association, charging favoritism toward some member companies.** Page 6

Business

Many biotechnology firms enter the new decade with hefty revenue gains and increased product sales, but few show a profit because of R&D and operating costs. **Page 9**

Science/Technology

Rapid route to producing and screening antibody fragments is breaking new ground and may soon replace hybridoma technology in many applications. **Page 18**

Low-cost method for catalytic asymmetric epoxidation of unsubstituted olefins has been developed by chemists at the University of Illinois, Urbana-Champaign. **Page 20**

Books

"Ozone Crisis" by Sharon L. Roan is a successful history of ozone depletion and the chlorofluorocarbon controversy, but falls down on reasons for lag time in response; "Dust Explosions" by W. Bartknecht is an up-to-date reference for those concerned with producing, storing, or transporting dusts. **Page 21**

ACS News

The society recently expressed views to the House on changes to laws governing disposal of hazardous wastes as well as on the need for more funds for fossil energy R&D. **Page 24**

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Government

National Institute of General Medical Sciences, source of most NIH chemistry research funds, reassesses priorities under tighter funding policies. **Page 13**

Chemical & Engineering News
1155—16th St., N.W., Washington, D.C. 20036
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Published by
AMERICAN CHEMICAL SOCIETY
(202) 872-4600; TDD (202) 872-8733
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Subscription Rates 1990. Printed editions: nonmembers U.S. 1 yr. $60, 2 yr. $108, outside U.S. 1 yr. $93, 2 yr. $174. Air freight rates available on request. Rates above do not apply to nonmember subscribers in Japan, who must enter subscription orders with Maruzen Co. Ltd., 3-10 Nihonbashi 2-chome, Chuo-ku, Tokyo 103, Japan. Tel: (03) 272-7211. Single copies: Current $9.00. Rates for back issues and volumes are available from Microforms & Back Issues Office, ACS, 1155—16th St., N.W., Washington, D.C. 20036. Back and current issues available on microfilm and microfiche. Rates on request from Microform Program, ACS.

Chemical & Engineering News (ISSN 0009-2347) is published weekly except for the last week in December by the American Chemical Society at 1155—16th St., N.W., Washington, D.C. 20036. Second-class postage paid at Washington, D.C., and additional mailing offices. POSTMASTER: Send address changes to Chemical & Engineering News, Membership & Subscription Services, P.O. Box 3337, Columbus, Ohio 43210. ACS assumes no responsibility for the statements and opinions advanced by the contributors to its publications.

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LETTERS

CHEMICAL SAFETY

Alkylaluminum fluoroalkoxides

SIR: In recent years, Texas Alkyls has been interested in organoaluminum compounds containing heteroatoms. Alkylaluminum compounds containing haloalkyl groupings were of particular interest because of their potential as catalyst modifiers in Ziegler-Natta olefin polymerization. Brian L. Goodall first reported an alkylaluminum fluoroalkoxide in 1981 at a symposium on transition-metal-catalyzed olefin polymerizations. Goodall described the effect of diethylaluminum 2,2,2-trifluoroethoxide (DEAL-FE) on model systems for Ziegler-Natta catalysts.

A variety of alkylaluminum fluoroalkoxides, including DEAL-FE, was synthesized at Texas Alkyls and tested as cocatalysts in olefin polymerization over a period of two years without incident. Preparations sometimes included purification via vacuum distillation at temperatures up to about 100 °C. Recently an explosion occurred in a syringe needle when one of our chemists was transferring a small quantity of DEAL-FE. Fortunately, because he was wearing the appropriate safety gear (face shield, fire-retardant lab coat, and gloves), the chemist was not injured. Subsequent to the incident, storage containers of alkylaluminum fluoroalkoxides at Texas Alkyls were checked for signs of decomposition. All containers, originally under a nitrogen pad of ≤3 psig, showed pressures of 40 psig or more after having been stored for several months, indicating slow decomposition even at ambient temperature.

Tests were conducted to investigate causes of the incident. Results showed that neat DEAL-FE begins to undergo slow, exothermic decomposition at about 75 °C. Above 100 °C, decomposition occurs violently. The power of neat DEAL-FE decompositions was found to be comparable to that of explosives. Further, the tests showed neat DEAL-FE to be shock sensitive. A 25% solution of DEAL-FE in heptane was subjected to the same battery of tests. The solution did not decompose violently on heating to about 190 °C, nor did it show shock sensitivity.

We urge that alkylaluminum fluoroalkoxides be produced only as dilute (≤25%) hydrocarbon solutions. Extreme caution should be used to ensure that such solutions are not concentrated in the course of handling to avoid the possibility of explosion from exposure to high temperatures or shock.

D. B. Malpass
Texas Alkyls Inc., Deer Park, Tex.

Ammonia does burn

SIR: The letter by Ernest J. Tews (C&EN, Jan. 15, page 2) highlights a problem with the meaning of familiar terms as defined in dictionaries of common usage, as used every day in ordinary speech and writing, and as defined technically. Whether or not ammonia is nonflammable or not depends on how the term is defined.

The term combustible is the most basic adjective relating to burning behavior. As defined by Webster (1979), and over the past 40 years or so, combustible applies to any material that "undergoes oxidation accompanied by the evolution of heat and light"—namely, any material that ignites and burns. Neither burn nor combustible implies a rate of reaction.

The word flammable, however, does imply a rate, and a flammable material is any combustible material that is "capable of being easily ignited and of burning with extreme rapidity." Conversely, a nonflammable material is "one that is not easily ignited and does not burn rapidly if ignited." To that extent ammonia is nonflammable. Of course, these definitions assume normal atmospheric conditions, not oxygen-rich or high-temperature environments such as mentioned by Tews.

Unfortunately, in popular usage flammable and combustible are more and more being used as synonyms, as are nonflammable and noncombustible, so that eventually the dictionary distinction between the meanings of the terms will be lost. This is reflected in Tews' letter.

To complicate matters, the wording used by the U.S. Department of Transportation to classify materials that are hazardous, primarily because of their burning behavior, does not follow either popular usage or dictionary definitions. In the Code of Federal Regulations (49 CFR 172.102) the burning behavior of materials is classified for labeling pur-

Correction

• March 12, page 19: Plastics contribute 3576 tons of lead to municipal solid waste streams, not 320 million tons.

Many Biotech Companies Enter '90s With Sharply Higher Revenues

Increased product sales are leading to hefty revenue gains, but with R&D and operating costs still high few firms reported profits for 1989

Ann M. Thayer,
C&EN Northeast News Bureau

With the start of a new decade, the health of the biotechnology industry in the 1990s is a topic of much speculation. If the close of the past decade is any indication, the industry is moving slowly toward profitability. Revenues in 1989 were up sharply for many biotechnology companies, with increased product sales contributing more significantly to income. However, the industry as a whole is not yet showing a profit.

According to a 1989 survey of nearly 500 biotechnology companies by Ernst & Young, a San Francisco-based consulting firm, only about one fourth of biotechnology companies are reporting net profits. But, more than 50% of all companies are seeing some improvement in performance in terms of smaller losses or larger profits than in previous years.

Similar trends are observed in a group of 35 companies sampled by C&EN. Combined 1989 revenues totaled slightly more than $1.2 billion, an increase of 33% over 1988. In addition, in 1989, these companies reported a combined loss of $175 million. Larger companies, including Amgen, Biogen, Collagen, and Genentech—with a few major products among them—saw the greatest increases in revenues and earnings. For some companies reporting a net income, 1989 marked the first year of profitability.

Sales account for about two thirds of revenues for those companies marketing products. Total sales reached nearly $600 million in 1989 for 20 of the 35 companies reporting product sales. This 53% increase over 1988 sales is higher than the industry average of 33% growth in sales from the survey by Ernst & Young, which determined that 74% of all companies have product sales.

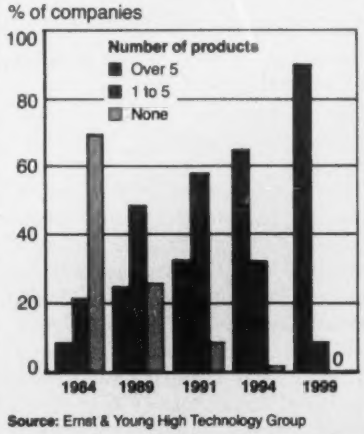
Contract research and collaborative R&D agreements provide the second most significant source of revenue for most companies. R&D spending averages 63% of sales in the biotechnology industry. Biotechnology companies in the area of therapeutics and agriculture can easily have R&D expenses at levels of more than 100% of sales. The norm for R&D spending in the pharmaceutical industry is 16% of sales.

Analysts predict that the 1990s will bring an increased flow of major biotechnology products. Introducing at least one new, and often a first, product is the goal of most companies in the near future. As many companies approach the final stages of product development and preparation for marketing, expenses increase markedly and earnings can drop dramatically. Cetus reported a net loss of more than $55 million in 1989, in preparation to launch its interleukin-2 product, which is awaiting Food & Drug Administration approval. Genetics Institute reported a net loss of nearly $29 million from delays in an anticipated licensing agreement, costs in preparing to market its erythropoietin (EPO) product awaiting FDA approval, and a contractual dispute related to EPO production. EPO is a protein that stimulates the production of red blood cells and is used to treat anemia.

EPO was approved for sale in June 1989, but premarketing expenses in the first half of the year offset Amgen's nearly $100 million in sales of the product. The company reported modest net earnings for 1989 and is facing a forced cross-licensing agreement with Genetics Institute on EPO in 1990 (C&EN, March 19, page 9). The company probably will continue to face high costs in preparation for the launch of its next big product, a granulocyte colony stimulating factor used for the production of white blood cells.

One biotech company well on its way is Genentech, of Thousand Oaks, Calif. With just two products, Genentech accounted for more than half of 1989 product sales for the 20 companies reporting sales. The company led the industry with $196 million in sales for Activase, the blood clot dissolving agent tissue plasminogen activator (TPA), and with $123 million in sales for Protropin, a human growth hormone. Despite being the largest and most profitable of companies, Genentech sent shock waves through the biotech-

Number of biotech products in market to rise



Source: Ernst & Young High Technology Group

Few biotech companies were profitable in 1989

$ Thousands	Revenues[a]	Earnings	Change from 1988 Revenues	Change from 1988 Earnings	Profit margin[b] 1989	Profit margin[b] 1988
Amgen	$155,729	$3,759	103%	191%	2%	2%
Applied Biosciences	57,690	4,930	86	31	9	12
Biogen	40,894	3,214	35	def	8	def
Biotech Research	17,112	1,485	4	-1.4	9	9
Calgene[c]	32,012	-6,574	25	def	def	def
California Biotechnology	15,832	-8,217	-6	def	def	def
Cambridge BioScience	8,572	-8,478	94	def	def	def
Calgene	2,753	-5,219	24	def	def	def
Centocor	76,963	115	22	-85	0.2	1
Cetus	28,704	-55,781	-16	def	def	def
Chiron	40,653	-21,629	15	def	def	def
Collagen	51,998	3,624	37	212	7	3
Crop Genetics	2,979	-6,053	-6	def	def	def
Cytogen	7,468	-13,956	27	def	def	def
Damon Biotech	5,997	-3,058	2	def	def	def
DNA Plant Technology	12,890	-2,948	60	def	def	def
Ecogen	2,939	-8,179	-55	def	def	def
Enzo Biochem	20,387	-4,382	63	def	def	def
Enzon	7,726	-3,563	166	def	def	def
Genentech	400,455	43,961	20	114	11	6
Genetics Institute	43,644	-28,737	47	def	def	def
Genzyme[d]	34,285	-5,704	33	def	def	3
Immunex	28,166	-6,979	27	def	def	3
Immunogen[e]	367	-3,727	-5	def	def	def
Integrated Genetics[f]	13,591	3,824	87	def	28	def
Liposome	3,761	-7,620	-16	def	def	def
Molecular Genetics	4,609	952	66	def	21	def
Mycogen	10,179	-1,403	74	def	def	def
Praxis Biologics[g]	11,971	-7,530	128	def	def	def
Repligen	12,044	-1,589	45	def	def	def
Ribi ImmunoChem	1,240	-2,891	-4	def	def	def
Synbiotics	7,194	-5,049	-5	def	def	def
Synergen	14,796	-1,311	103	def	def	def
T Cell Sciences	10,991	-1,203	55	def	def	def
Xoma[h]	19,230	-18,878	32	def	def	def

a Includes sales, contract research, royalty, and interest revenues. b After-tax income as percentage of sales. c Consolidated figures to include merger with Ingene in November 1989. d Third- and fourth-quarter results include acquisition of Integrated Genetics. e Results for two quarters after going public in August 1989. f Results for first and second quarters before being acquired by Genzyme. g First three quarters, acquired by American Cyanamid in November 1989. h Consolidated figures to include merger with Ingene in November 1989. def = deficit.

nology and financial communities when it decided it was necessary to sell a 60% interest to Roche Holding Ltd, whose main operating arm is Hoffmann-La Roche, the large Swiss chemicals and pharmaceutical firm.

Roche's investment will allow the company to operate independently while providing it with $492 million in capital to expand R&D efforts. An investment of this size effectively removes Genentech from having to respond to public financial markets, allowing it to focus on long-term R&D efforts. Although the company is marketing two major products, Activase is expected to receive very stiff competition in the coming years from less expensive drug treatments.

For most companies, sources of financing remain the major concern. According to the Ernst & Young survey, 62% of all companies will need major financing of a few million dollars each by the end of 1990 and 90% will need financing by the end of 1991. For some companies the problems are imminent: 59% of small companies, 35% of mid-size, and a few percent of large companies will survive less than 12 months without immediate financing.

In general, companies seek support from three sources—public equity markets, R&D or manufacturing alliances with large companies, and mergers. Cash flow problems affected several companies in 1989 and are leading to what some believe are the first stages of consolidation in the industry. Bio Response, Hayward, Calif., unable to find the cash to cover $22.4 million worth of debentures tendered in 1989, declared bankruptcy in September. The company, which produces proteins by mammalian cell culture methods for use in therapeutic drug products, was acquired for $9 million by Baxter Healthcare, the U.S. operating subsidiary of the large Baxter International health care company.

Large pharmaceutical companies can use an acquisition of a smaller company as a means to obtain an established technology and enter the biotechnology arena. As is often the case, a relationship between the biotechnology and pharmaceutical company may already exist. The recent acquisition of Damon Biotech, Needham Heights, Mass., by Abbott Laboratories for $9.4 million is an example. Damon Biotech had agreed to produce genetically engineered urokinase, a competing drug with TPA, for Abbott. In April 1989, the company reported it had sufficient cash to operate for about 12 months and expressed concern about future cash availability.

Similarly, American Cyanamid acquired Praxis Biologics, Rochester, N.Y., in November 1989 in an exchange of $238 million worth of shares. Praxis reported losses of more than $7 million in both 1988 and 1989. However, the company had product sales of more than $8 million on its Hibtiter vaccine for bacterial meningitis, one of the first biotechnology drugs to receive FDA approval. The company was seeing lower than expected sales, increasing competition, and high costs in bringing its second product to market.

Not all acquisitions or mergers have been among large pharmaceutical and smaller biotechnology

companies. Calgene, based in Davis, Calif., and one of the larger agricultural biotechnology companies, acquired its neighbor and rival, Plant Genetics, in a $12 million stock transaction completed in July 1989. Mycogen, San Diego, Calif., another rapidly growing agricultural biotechnology company, bought the commercial and agricultural products division of Safer for an investment of $5.5 million. In the area of therapeutics, Xoma, Berkeley, Calif., acquired Ingene in November. Genzyme, Boston, merged with Integrated Genetics, Framingham, Mass., in mid-1989. Mergers are being used increasingly by biotechnology companies as a means to expand resources in their push toward marketing products.

Unlike the acquisition of a biotech firm by a large, capital-rich pharmaceutical company, acquisition of one biotechnology company by another can strain finances and often requires betting on future prosperity. For instance, Calgene and its newly acquired subsidiary, Plant Genetics, reported increased revenues but a net loss for 1989. The company expects a loss through 1990 with the continuing costs of product development and increased operating expenses after the merger. Having raised $27 million in an August 1989 stock offering and established a $10 million credit agreement early in 1990, the company plans to expand field trials of its herbicide-resistant crops.

In a move to raise at least $15 million in capital to bring its products to market, Ecogen, an agricultural biotechnology company based in Langhorne, Pa., recently appointed an investment banker to investigate the sale of all or part of the company. The company predicts bankruptcy in the next six months if new capital is not brought in. Ecogen has two biopesticide products that have received EPA registration, a third product nearing approval, and several more under development. The company lost more than $8 million in 1989 on decreased revenues of $2.94 million.

More recently, in mid-March Ecogen disclosed two investments in the company. One was a sale of $1.5 million worth of stock to a single private New York investor. The other was a sale of $500,000 worth of stock and the awarding of exclusive distribution rights for its biopesticides in Taiwan to Jia Non Enterprises. Over seven years, the Taiwanese company will pay Ecogen up to $2.7 million in royalties and has the option to purchase another $500,000 in shares.

With its acquisition of Ingene, Xoma reported a net loss of nearly $19 million in 1989 resulting from increased expenses and its push toward commercialization of two products based on monoclonal antibodies. In April 1989, Xoma raised $57.5 million on an issue of debentures redeemable in 2014. The company has applications pending with FDA for approval of Xomen E5, used to treat gram-negative sepsis, and Xomazyme H65, used to treat graft versus host disease in bone marrow transplants.

Companies with successful product launches may become self-sustaining companies in the future and find public markets more willing to invest. A long-stated goal of biotechnology companies has been to operate as independent, vertically integrated biopharmaceutical firms. Most companies currently rely on manufacturing alliances to market their products.

One company that has successfully used its strategic alliances is Biogen, based in Cambridge, Mass. The company has developed at least five major biotechnology drugs and has licensed them to large worldwide pharmaceutical manufacturers for marketing. In 1989, the company reported its first profitable year. However, in light of industry goals, companies will have to balance short-term cash returns with long-term commitments to outside companies. An increased number of strategic alliances throughout the 1990s, concludes Ernst & Young, may lead to a smoother consolidation of the biotechnology industry in the future. □

Product sales are major part of 1989 revenues

$ Thousands	Product sales	Change from 1988	% of revenues	R&D costs	R&D as % of sales
Amgen	$ 99,427	3825%	64%	$ 63,166	64%
Biogen	24,725[a]	28	61	28,486	115
Calgene[b]	21,808	25	68	11,283	52
California Biotechnology	1,006[a]	–84	6	14,858	nm
Centocor	27,616	25	36	45,354	164
Cetus	4,468[a]	134	16	50,000[c]	nm
Chiron	4,934	304	12	46,100	934
Collagen	45,315	44	87	14,099	31
Crop Genetics	2,051	5	69	5,361	261
DNA Plant Technology	161[a]	164	1	11,985	nm
Genentech	319,000	22	80	159,000	50
Genetics Institute	na	—	—	59,426	na
Genzyme[d]	23,753	26	69	na	na
Immunex	4,276[a]	142	15	18,889	442
Liposome	54[a]	–78	1	8,027	nm
Molecular Genetics	120	199	3	2,229	nm
Mycogen	955	449	9	7,842	821
Praxis Biologics[e]	8,243	3335	89	8,456	103
Ribi ImmunoChem	728	23	39	1,794	246
Synbiotics	4,452	90	62	5,410	122
T Cell Sciences	3,336	24	30	na	na
Xoma[f]	na	—	—	25,617	na
TOTAL[g]	$569,140	53%	62%	$488,522	88%

a Includes royalties and licensing fees. b Consolidated figures for the year to reflect merger with Plant Genetics in July 1989. c C&EN estimate. d Last six months of year include acquisition of Integrated Genetics. e First three quarters, acquired by American Cyanamid in November 1989. f Consolidated figures for the year to reflect merger with Ingene in November 1989. g Totals and percentages for companies reporting both sales and R&D costs. nm=not meaningful, percentage greater than 1000. na=not available.

Chemical Research Funding Hit By Tight Budgets At NIH

National Institute of General Medical Sciences, source of most NIH chemistry research funds, changes priorities under new funding policies

Pamela S. Zurer, C&EN Washington

At the National Institutes of Health, most research funding for chemists comes from the National Institute of General Medical Sciences (NIGMS). In fiscal 1988, for example, NIGMS awarded $86 million to departments of chemistry—71% of total NIH funding for chemistry and not a whole lot less than the amount supplied by the National Science Foundation's chemistry division. It's no surprise, then, that chemists are worried that NIGMS, like the rest of NIH, is facing severe budget constraints on the number of new grants it can fund.

Given a budget that has been just keeping up with inflation, large commitments to continue funding ongoing grants, and the escalating cost of the average grant, the number of approved applications that NIGMS can support has plummeted.

"For most of the '70s and the '80s, NIGMS funded close to 40% of approved applicants," says the institute's deputy director Marvin Cassman. "Last year [fiscal 1989] it was 29%, and this year our projected value is 23% and may well turn out to be lower. That's one chance in five for all applications coming into the system. For certain categories of applications there's an even poorer probability of success.

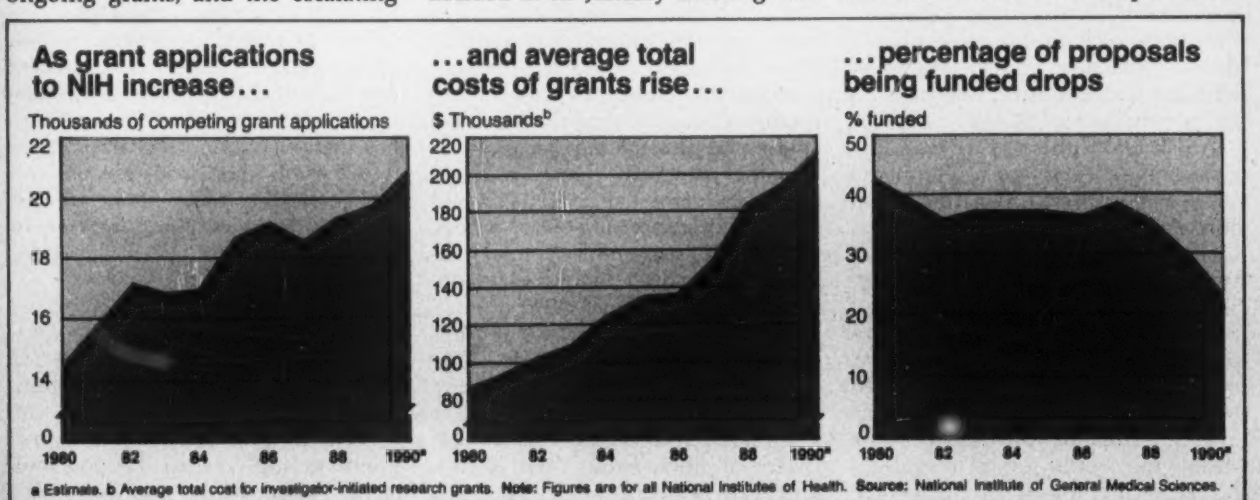
"There's always a line that you draw when you run out of money. And the people on one side of that line are very close to the people on the other side. But for the first time, the people on the wrong side of the line are almost as good as the best people we're funding. That's very hard to take."

NIGMS is responding to the problems caused by extremely tight money by implementing three new policies. The National Advisory General Medical Sciences Council, which sets policy for the institute, decided at its January meeting that NIGMS staff should—in certain cases—consider factors other than scientific merit in making funding decisions.

The staff has been instructed to give special consideration to highly rated applicants who have no other source of research funds. At the other end of the scale, applications from researchers whose total grant support exceeds $500,000 will be given extra scrutiny. And renewal applicants will generally be held to a 10% increase in budget over their previous grant.

"We're not happy about having to do any of these things," Cassman says. "It's a question of how to assess our priorities when faced with a situation where the grants that we are not funding are almost as good as the best grants that we are funding."

NIGMS's support for chemistry research is substantial, but pinning down its exact extent is difficult. The figures for money awarded to departments of chemistry represent a minimum, for much of the chemical research underwritten by the institute is carried out in departments

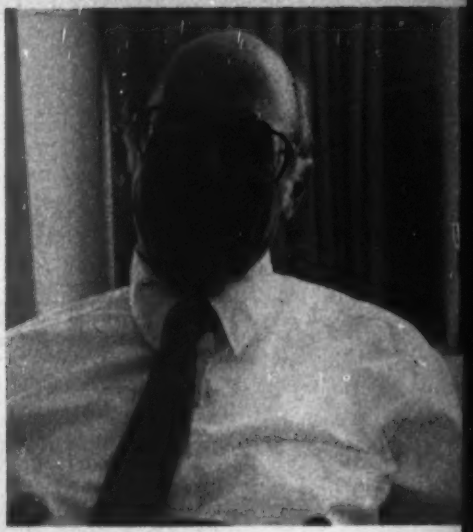


a Estimate. b Average total cost for investigator-initiated research grants. **Note:** Figures are for all National Institutes of Health. **Source:** National Institute of General Medical Sciences.

of biochemistry or molecular biology or in medical schools.

"If you include in your definition of chemistry every research area set out in the National Academy of Sciences' report 'Opportunities in Chemistry,' that would account for practically the entire institute's budget," Cassman says. In fiscal 1989, the institute spent more than $541 million on research project grants and expects to give out about $561 million in fiscal 1990.

The bulk of NIGMS's funds that go to chemistry as it is more traditionally defined spring from three administrative areas within the institute: the pharmacological sciences program, the cellular and molecular basis of disease program, and the biophysics and physiological sciences program.



Cassett (left): training programs vital. Cassman: one-in-five funding chance. Jones: competing pool is shrinking

The focus at NIGMS is very different from the other NIH institutes, which specialize in specific diseases or organs. NIGMS's goal is to support the basic research that underpins other health-related investigations.

"Our director's philosophy is that we support investigator-initiated research in many areas, as long as it's good science," says Christine Carrico, director of the pharmacological sciences program. "We're a basic science institute and generally the direction the research is going to go is determined by what the scientific community is doing."

Adds Michael Rogers, scientist administrator in the same program: "We try to pick out the science that's the best and fund that, regardless of whether it's chemistry, pharmacology, genetics, or whatever."

About two thirds of pharmacological sciences' funds go to biorelated chemistry projects. "We fund a sizable amount of organic chemistry, including organic synthesis, total synthesis, reaction methodology, and natural products chemistry," Rogers says. "We also have a big portfolio of inorganic chemistry, looking at metallochemistry related to metalloproteins and metalloenzymes." The program also funds a sizable number of grants in molecular recognition, biomimetic-type chemistry, artificial enzymes, photochemistry, and peptide and nucleic acid chemistry.

The pharmacological sciences program also has an anesthesiology branch, which supports research into the molecular mechanisms of how anesthetics act, as opposed to general whole-organism studies.

"The only real restriction—and that is also not a hard and fast one—is that the research has to be biologically related," Carrico says. "There are probably a few grants we support where you have to go through some mental gymnastics justifying the biological relevance, but by and large because it's NIH the research we support should be biologically related."

Last year the pharmacological sciences program put out a specific request for grant proposals in basic chemistry in support of acquired immune deficiency syndrome-related studies, an unusual move at an institute that generally does not solicit proposals. However, NIGMS had been given a specific pool of money to fund fundamental chemical research that could benefit development of drugs against AIDS.

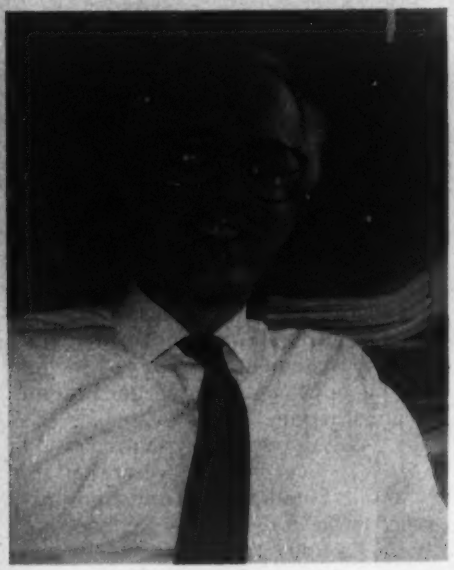
Among other areas, the request for AIDS-related applications suggested such research fields as chemistry for linking small molecules to natural macromolecules, chiral synthesis of nucleosides, and design and synthesis of selective DNA cleaving compounds. The institute received close to 50 applications by the Dec. 1 deadline and expects to fund seven to 10 grants with a total cost of up to $1.5 million.

Another NIGMS unit that funds a significant amount of chemistry is the molecular section of the cellular and molecular basis of disease program. About one quarter of the 365 grants that section is funding this year support investigators in chemistry departments. Another third goes to biochemistry departments.

"A lot of work that is supported through this program is concerned with catalysis, mechanisms of enzyme action, regulation of catalytic properties, metabolic transformations, and metabolic pathways," says Warren Jones, chief of the molecular section.

Much of the rest of the research his section supports could also be called chemistry, Jones says. "When all is said and done, every process that sustains life is based on chemistry," he points out. "This institute has historically and steadfastly said it will try to fund good research and not be terribly picky about what it is. We've had a very catholic view of what we'd support. The criterion is: 'Is it good science?' "

In the biophysics section of NIGMS's biophysics and physiological sciences program, 266 out of 582 grants, totaling about $36 million, are in chemistry departments, according to James Cassatt, the program's acting director. "If you look at the subject matter and ask what's



different about our grants that go to chemistry departments as opposed to biology or molecular biology departments, the answer is 'not much,'" he says.

Among the research areas the biophysics program supports are analytical chemistry and spectroscopic techniques. It also funds research into the biophysical properties of nucleic acids and proteins.

Other sections of the biophysics program support x-ray crystallography and analysis of proteins, nucleic acids, and related model systems by NMR. The NMR unit was created just a few years ago in response to progress in the field.

The biophysics program that is most dominated by chemist-investigators supports theoretical studies of proteins and nucleic acids. "These people are doing very fundamental studies," Cassatt says. "You'd find very few molecular biology departments that would house people like these—they are hard-core chemists."

In addition to its research grants, the biophysics and physiological sciences program administers a new training fellowship that draws heavily from chemistry departments. "It became clear a few years ago that there were insufficient numbers of structural biologists," Cassatt adds. "That is, people trying to understand the relationship between biologically important macromolecules and disease states.

"The whole area of computer-aided drug design really began with an understanding of structural biomolecules. It also appeared to be a fruitful area for investigating possible therapies for AIDS. But all this depends on the ability to train people in structural biology."

In designing the new training program, NIGMS encouraged universities to draw from pools of students beyond traditional biology departments. The fellowships are now supporting more than 200 trainees at 27 schools that have set up interdisciplinary programs.

"Some of our most successful programs have tried to attract people from chemistry departments, physics departments, and even math and engineering departments," Cassatt says. "These are students who traditionally have had the kind of quantitative training that's necessary for success in structural biology. They may be weak on biology, but it's our feeling that—with many exceptions—it's easier to take someone in the quantitative sciences and teach them biology than vice versa."

All the NIGMS programs are facing the same tight funding squeeze. Once money is set aside from the current year's budget to pay for the ongoing grants that were previously funded (so-called noncompeting applications), there is little left for new grants (competing applications).

In fiscal 1988, NIGMS was able to fund slightly less than 1000 competing grants. In fiscal 1989, that number dropped to about 760 and is expected to decline further to about 630 this fiscal year.

"That's what's got everybody so discouraged," Jones says. "The pool of money has been growing a bit over that period but the additions to the budget have gone primarily to cover inflation. Our total number of grants is holding roughly constant, but because we were very successful in putting out new grants in the mid-1980s, it means that if the total pool doesn't grow the competing pool has to shrink."

Thus, the award rate for those applying to NIH for funds for the first time is much worse than the overall award rate of roughly 20% in fiscal 1990. Renewal applications inevitably have a better shot, according to deputy director Cassman.

"Renewal applications are all prescreened," he notes. "They were funded once already and that means somebody thought they were pretty good to begin with. Historically, they have always had a better probability of success. It used to be about 50%, but now it's about 30%."

Applications from investigators with no track record are the ones that are really suffering, according to Cassman. Those grant proposals often are from young researchers just beginning an independent career.

Cassman says it is not surprising or even undesirable that the peer-

Carrico (left) and Rogers seek to fund best basic pharmacological research

National Institute of General Medical Sciences' budget is only keeping pace with inflation

$ Millions	1991[a]	1990[a]	1989[b]	% change 1990–91
Genetics	214.8	208.6	209.5	3%
Cellular and molecular basis of disease	204.6	193.9	189.8	6
Biophysics and physiological sciences	151.8	144.5	133.4	5
Pharmacological sciences	103.5	99.2	92.5	4
Minority biomedical research support	32.3	29.8	28.1	8
Minority access to research careers	13.4	10.7	9.1	25
Research management, other	25.1	25.4	21.5	−1
TOTAL	745.5	712.1	683.9	5%

Note: Programs that provide major support for research in chemistry departments are printed in color. a Estimate. b Actual. Source: National Institute of General Medical Sciences

review system favors renewal-grant applicants. People who have done well in the past will inevitably have an edge. The discrepancy was less painful, however, when there was enough money to fund both groups reasonably well.

"The best estimate I can get for applications coming in from first-time applicants—primarily young investigators starting out—is an award rate on the order of 11%," Cassman says. "That is an outrageously low number.

"What that means is the odds for a kid coming into his first academic position who is starting up a laboratory are a little better than one in 10. All things considered, the universities might be better advised to take the money that it costs in time and effort to send in a proposal, give it to whoever is applying, and tell him to go to Las Vegas. The odds are probably better than 10-to-one there."

Another group of applicants suffering from the low-award rate is made up of established investigators running small laboratories that get by with only one grant, according to Cassman. That practice was more common before many researchers began hedging their bets by having multiple grants, but many good scientists have not chosen to expand.

The first of the NIGMS advisory council's three recent recommendations is designed to address the crisis facing those two groups of applicants. It suggests that, given two proposals of similar merit, NIGMS should give preference to investigators with no other sources of support. That means that applications with better priority scores—the numerical ranking given proposals by peer reviewers—could be passed over in favor of ones that scored not quite so well.

Cassman explains, however, that all the applications in the range of priority scores affected are so good that differences of a few points are not really meaningful anyway. "We are now cutting off funding within a group of such high quality that it's extremely difficult to measure any difference between one grant and another," he says.

"We felt and our council felt that if we didn't protect not only the younger investigators, to allow them entry into the system, but also high-quality smaller laboratories, we'd lose something significant in the breadth of research that we can support."

The second NIGMS council recommendation is that the staff look very carefully at applicants that have more than $500,000 in support from any source. The impetus behind this policy is that large laboratories often have the wherewithal to spin off projects from existing grants.

"We have gotten applications where, although the proposal was evaluated as outstanding, it wasn't all that different in its target from another, already funded project," Cassman says. "It was another system, another organism, another enzyme of a similar kind. The question is: Do we want to fund another one of those as compared to a new application from a new investigator?"

The new policy in part reflects a recognition by NIGMS of the concern shown by a few of the NIH study sections (peer-review groups), according to Cassman. Study sections are supposed to judge only the quality of science in a proposal, not make funding decisions. Lately some have taken it upon themselves to do both, distorting the system in Cassman's opinion.

"We have had a few recent applications, which would have been outstanding in a normal review process, where the study section gave terrible priority scores," he says. "They said straight out in the summary statement of their report that [the applicants] were getting too much money."

"We are being very cautious about this [policy] because we are talking about outstanding investigators," Cassman adds. "Secondly, we don't like to tinker with peer-review decisions that aren't at the margin, which is what we were talking about in the first set of recommendations. But I think the council felt that given the circumstances we have no choice. It's an issue of equity."

The last advisory council recommendation involves budget increases for ongoing grants that have come back for renewal after peer review, known as competing continuations. With one exception, increases are to be held to 10%, plus whatever equipment is required.

The exception to the 10% ceiling is for first-time reapplicants who are eligible for renewal after their first grant. "Very often first renewals are an opportunity for an investigator to expand to a reasonable level after having been held to a comparatively small dollar level," Cassman points out. "We don't want to eliminate the opportunity for people really to get a foothold in their field."

NIGMS is moving very gingerly in implementing these new policies aimed at equitably distributing the pain of insufficient funds. "Obviously we need to examine the effects and consequences," Cassman says. "But we are putting them in effect now because, to be quite honest, there are people who can't wait for next year. They're going to die if they don't get their money now. And let me assure you, there are a large number of people for whom we can do nothing that I feel even worse about." □